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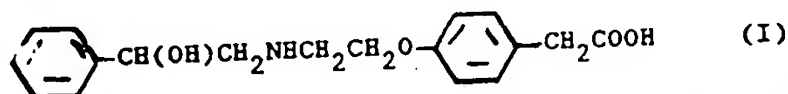
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(54) 2-Hydroxy-2-phenylethylamine derivatives as beta-3-adrenoceptor agonists.

(57) Compounds of the formula (I):

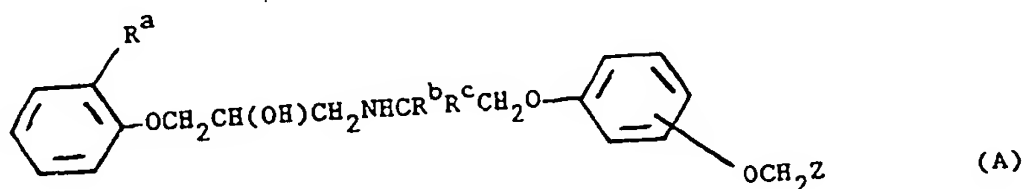


and bioprecursors and pharmaceutically acceptable salts thereof are described as β_3 -adrenoceptor agonists having anti-obesity, hypoglycaemic and related therapeutic utilities. Processes for their preparation are described as are compositions containing them.

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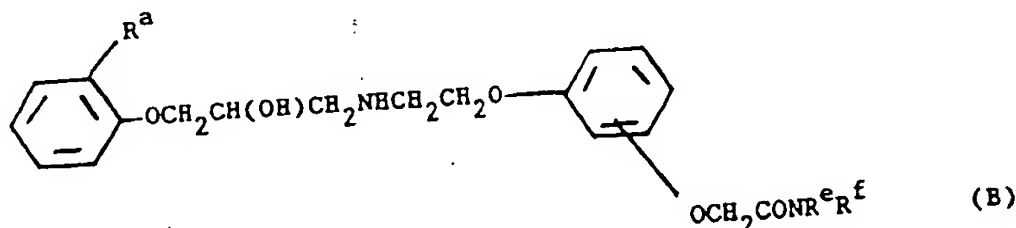
The present invention relates to 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid and bioprecursors thereof. This invention further relates to processes and intermediates for their preparation, to their use in methods of therapy and to pharmaceutical compositions containing them. The compounds of the present invention are β_3 -adrenoceptor agonists and are of value in disease conditions mediated through such adrenoceptors. Administration of the compounds of this invention to warm-blooded animals provides a thermogenic effect, that is thermogenesis is stimulated and administration of the compounds is of use, for example, in the treatment of obesity and related conditions such as mature onset diabetes associated with obesity. In addition, the compounds of this invention improve glucose tolerance in warm-blooded animals and are of use in combating disease conditions wherein such activity is beneficial for example they have hypoglycaemic activity. The compounds of this invention may also be used in the treatment of non-insulin dependent diabetes mellitus (NIDDM) and in conditions wherein insulin resistance is of importance such as hypertension, hyperlipidaemia and decreased fibrinolysis (Reaven's syndrome or Syndrome X).

The present applicants have conducted substantial research into β_3 -adrenoceptor agonists and, in particular into their thermogenic effect. Our own United States Patent 4772631 discloses compounds of the formula (A):



wherein R^a is hydrogen or fluoro; R^b and R^c are independently selected from hydrogen and C_{1-3} alkyl; and Z is hydroxymethyl or a group of the formula $-COR^d$ in which R^d is hydroxy, C_{1-6} alkoxy or amino.

Our own United States Patent 4940168 discloses compounds of the formula (B):



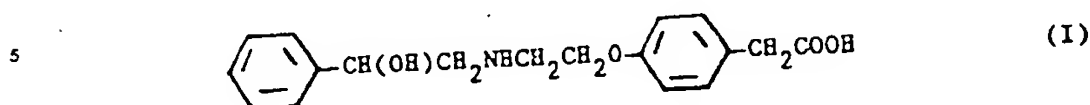
wherein R^a is hydrogen or fluoro and R^e and R^f are independently hydrogen or a variety of groups leading to secondary and tertiary amides. It is believed that compounds of the formula (A) wherein R^d is alkoxy or amino, and the compounds of the formula (B), are primarily bioprecursors that are effective via the corresponding oxyacetic acid; that is the compound of the formula (A) wherein R^d is hydroxy.

The present applicants identified the compound of the formula (A) wherein R^a - R^c were hydrogen and R^d was hydroxy as being of significant interest. However, this compound did not have an ideal profile of solubility and absorption characteristics. Accordingly, the present applicants developed a secondary amide bioprecursor of this compound. This secondary amide was introduced into human volunteer patients. Disappointingly, there was insufficient effect on metabolic rate in the clinic and this, in effect, pointed to insufficient efficacy of the free carboxylic acid at the β_3 -adrenoceptor.

Further investigations were performed and we have now discovered a compound which, surprisingly, provides significant thermogenic effects at doses which cause relatively few side-effects. It is understood that selectivity of thermogenic effect, for example lack of cardiac side-effects, is an important requirement for a useful therapeutic agent in the treatment of, for example, obesity and related conditions.

This compound of the present invention is a carboxylic acid and shows significant advantage over the above referred to secondary amide and free carboxylic acid. In particular, it has been shown to have full efficacy at β_3 -adrenoceptors, whereas the compound which had been administered to man was found to have low efficacy.

In addition, it has been shown to have surprisingly good solubility and absorption characteristics. Accordingly the present invention provides a compound of the formula (I):



or a bioprecursor or a pharmaceutically acceptable salt thereof.

10 Favourably the compounds of the formula (I) are in the form of a carboxylic acid or a pharmaceutically acceptable salt thereof. 4-[2-(2-Hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid and certain bioprecursors are amphoteric and may be used in the zwitterionic form, or as a pharmaceutically acceptable acid addition salt, or as a salt with a base affording a pharmaceutically acceptable cation. Particular examples of pharmaceutically acceptable acid-addition salts include, for example, salts with inorganic acids such as hydrohalides (especially hydrochlorides or hydrobromides), sulphates and phosphates, and salts with organic acids such as succinates, citrates, lactates, tartrates and salts derived from acidic water-soluble polymers. Particular examples of salts with bases affording a pharmaceutically acceptable cation include, for example, alkali metal and alkaline earth metal salts, such as sodium, potassium, calcium and magnesium salts, and ammonium salts and salts with suitable organic bases such as triethanolamine.

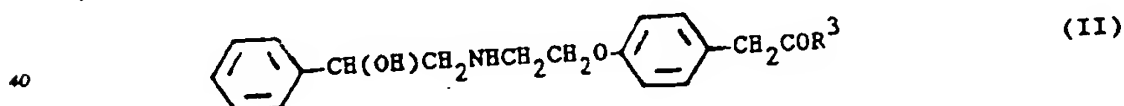
20 Bioprecursors are those pharmaceutically acceptable compounds that are degraded in the animal body to produce the parent acid. Such compounds can be identified by administering, for example orally to a test animal, the compound under test and subsequently examining the test animal's body fluids.

One class of bioprecursor is that of the corresponding ester bioprecursors of the carboxy group of 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid. Suitable esters include C₁₋₆alkyl esters, for example the methyl and ethyl esters.

25 Another class of bioprecursor is that of the corresponding ester bioprecursors of the hydroxy group (-CH(OH)-). Such esters include, as their acyl group for example, acetyl, propionyl, pivaloyl, C₁₋₆alkoxycarbonyl for example ethoxycarbonyl and phenylacetyl.

30 A further class of bioprecursor is that of the corresponding amide bioprecursors of the carboxy group of 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid. Suitable amides include, for example, amides of the formula -CONR¹R², wherein R¹ and R² are independently hydrogen, C₁₋₆alkyl, hydroxyc₂₋₆alkyl (wherein the hydroxy substituent is on other than the α-carbon), C₁₋₆alkoxy-C₁₋₆alkyl, phenylalkyl, allyl, cyclopropyl or cyclopentyl or the group -NR¹R² is morpholino, piperidino or pyrrolidino. In general amides, in particular wherein R¹ and R² are independently hydrogen, are primarily viewed as intermediates for the preparation of the corresponding carboxylic acid or ester.

35 A preferred class of bioprecursors is that of the formula (II):



wherein R³ is C₁₋₆alkoxy for example methoxy.

45 Bioprecursors of 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid may have a thermogenic effect in their own right and this is another aspect of the invention.

Especially preferred compounds of the invention are:

(R)-4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid;
 (R)-4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetamide;
 (R)-methyl 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetate;
 50 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid;
 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetamide; and
 methyl 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetate;
 and pharmaceutically acceptable salts thereof.

55 It will be appreciated that 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid and bioprecursors thereof contain one or more asymmetric carbon atoms and can exist as optically active enantiomers or as optically inactive racemates. The present invention encompasses any enantiomer, racemate and/or (when two or more asymmetric carbon atoms are present) diastereoisomer, which when administered in a therapeutic

amount provides a thermogenic effect in warm-blooded animals, it being well known in the chemical art how to prepare individual enantiomers, for example by resolution of the racemate or by stereospecific synthesis, and how to determine the thermogenic properties, for example, using the standard tests described hereinafter. It is preferred that the compounds of the present invention are provided in the (R) absolute configuration at the

5 -CH(OH)- group (under the Cahn-Prelog-Ingold rules).
In order to use a compound of the present invention or a pharmaceutically acceptable salt thereof for the therapeutic treatment of warm-blooded mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises
10 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid, or a bioprecursor thereof or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The pharmaceutical compositions of this invention may be administered in standard manner for example by oral or parenteral administration. For these purposes they may be formulated by means known to the art into the form of, for example, tablets, capsules, pills, powders, aqueous or oily solutions or suspensions, emul-
15 sions, and sterile injectable aqueous or oily solutions or suspensions.

In general compositions for oral administration are preferred.

The compositions may be obtained using standard excipients and procedures well known in the art. A unit dose form such as a tablet or capsule will usually contain, for example 0.1-500 mg of active ingredient, more suitably 10-250mg, and preferably 50-100mg of the compound of this invention.

20 The compositions may also contain other active ingredients known for use in the disease condition to be treated, for example appetite suppressants, vitamins, antihypertensives and hypoglycaemic agents such as sulphonylureas, biguanides and thiazolidinediones. It is understood that such compositions cover co-formulation, concurrent and sequential therapy of the two or more active ingredients.

In one aspect of the present invention, 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid or
25 a bioprecursor thereof may be formulated for oral administration in a sustained (or delayed) release composition, for example a matrix tablet formulation comprising insoluble or swellable polymeric filler, or a coated spheroid formulation.

When used to produce thermogenic effects in warm-blooded animals including man, 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid or a bioprecursor thereof or a pharmaceutically acceptable salt thereof as appropriate, will be administered so that a dose in the general range 0.002-20 mg/kg, suitably in the
30 range 0.02-10 mg/kg, and preferably in the range 0.5-5 mg/kg is administered daily, given in a single dose or divided doses as necessary, typically one to three times a day. However, it will be appreciated by those skilled in the art that dosage will necessarily be varied as appropriate, depending on the severity of the condition under treatment and on the age and sex of the patient and according to known medical principles.

35 In addition the compounds of the present invention lower triglyceride levels and cholesterol levels and raise high density lipoprotein (HDL) levels and are therefore of use in combatting medical conditions wherein such lowering (and raising) is thought to be beneficial. Thus they may be used in the treatment of hypertriglyceridaemia, hypercholesterolaemia and conditions of low HDL levels in addition to the treatment of atherosclerotic disease such as of coronary, cerebrovascular and peripheral arteries, cardiovascular disease and related con-
40 ditions.

Accordingly in another aspect the present invention provides a method of lowering triglyceride and/or cholesterol levels and/or increasing HDL levels which comprises administering, to an animal in need thereof, a therapeutically effective amount of 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid or a bioprecursor thereof or pharmaceutically acceptable salt thereof. In a further aspect the present invention provides a method
45 of treating atherosclerosis which comprises administering, to an animal in need thereof, a therapeutically effective amount of 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid or a bioprecursor thereof or pharmaceutically acceptable salt thereof. The compositions are formulated and administered in the same general manner as detailed above for producing a thermogenic effect. They may also contain other active ingredients known for use in the treatment of atherosclerosis and related conditions, for example fibrates such as
50 clofibrate, bezafibrate and gemfibrozil; inhibitors of cholesterol biosynthesis such as HMG-CoA reductase inhibitors for example lovastatin, simvastatin and pravastatin; inhibitors of cholesterol absorption for example beta-sitosterol and (acyl CoA:cholesterol acyltransferase) inhibitors for example melinamide; anion exchange resins for example cholestyramine, colestipol or a dialkylaminoalkyl derivative of a cross-linked dextran; nicotyl alcohol, nicotinic acid or a salt thereof; vitamin E; and thyromimetics.

55 In a further aspect the compounds of the present invention stimulate the "atypical" β -adrenoceptors in the gastrointestinal tract and therefore inhibit gastrointestinal motility. They may be of use in combatting medical conditions wherein stimulation of "atypical" β -adrenoceptors in the gastrointestinal tract is thought to be beneficial, such as in combatting medical conditions wherein inhibition of gastrointestinal motility is thought to be

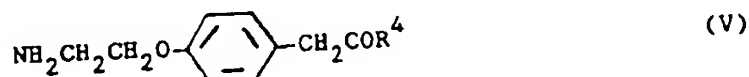
of value. Thus they may be of use for example in the treatment of inflammatory bowel disease (IBD) (such as Crohn's disease and ulcerative colitis), irritable bowel syndrome (IBS), non-specific diarrhoea and dumping syndrome.

Accordingly the present invention provides a method of stimulating the "atypical" β -adrenoceptors in the gastrointestinal tract which comprises administering, to an animal in need thereof, a therapeutically effective amount of a compound of the present invention.

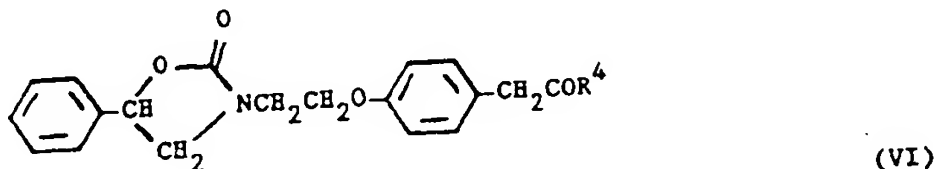
In a further aspect the present invention provides methods of inhibiting gastrointestinal motility, treating IBD, treating IBS, treating non-specific diarrhoea and treating gastric emptying in dumping syndrome which comprise administering to an animal in need thereof, a therapeutically effective amount of a compound of the present invention.

In a further aspect the present invention provides a process for preparing 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid or a bioprecursor thereof or a pharmaceutically acceptable salt thereof which process comprises:

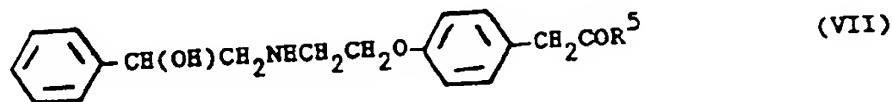
a) reacting a compound (III) or (IV) with a compound of the formula (V):



wherein $-\text{COR}^4$ is carboxy or its bioprecursor and L is a displaceable group; or
b) hydrolysis of a compound of the formula (VI):



wherein COR^4 is as hereinbefore defined; or
c) for 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid hydrolysing a compound of the formula (VII):



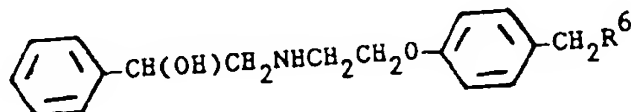
wherein R^5 is a hydrolysable group;
d) reacting a compound of the formula (VIII) with a compound of the formula (IX):





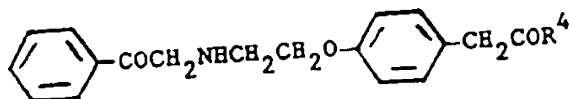
(IX)

wherein $-COR^4$ is as hereinbefore defined and L' is a displaceable group;
e) deprotecting a compound of the formula (X):



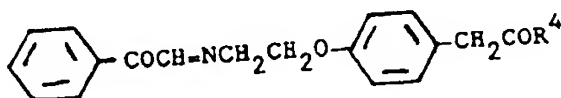
(X)

wherein R^6 is a protected derivative of a group $-COR^4$;
f) converting 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid into a bioprecursor, or vice versa, or converting a bioprecursor of 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid into another bioprecursor of 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid;
g) reducing a compound of the formula (XI):



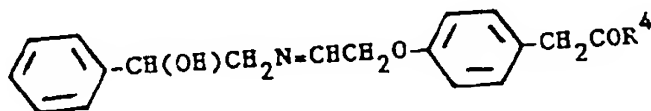
(XI)

wherein $-COR^4$ is as hereinbefore defined;
h) reducing a compound of the formula (XII):



(XII)

wherein $-COR^4$ is as hereinbefore defined;
i) reducing a compound of the formula (XIII):



(XIII)

wherein COR^4 is as hereinbefore defined; and wherein any functional group is optionally protected and thereafter if necessary;

(i) removing any protecting groups;

(ii) forming a pharmaceutically acceptable salt.

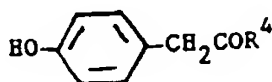
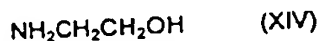
Protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question, and may be introduced by conventional methods.

Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

A particular protecting group is a hydrogenolysable group present on the nitrogen atom of $-CH(OH)CH_2NCH_2CH_2O-$. Suitably the protecting group is benzyl or a substituted benzyl group. Such a protecting group may be removed in conventional manner using methods of catalytic hydrogenation, for example palladium on carbon catalysts in an atmosphere of hydrogen. Suitable conditions include ambient and elevated temperatures and pressures in a solvent such as a C_{2-6} -alcohol for example ethanol or propan-2-ol. Compounds corresponding to formula (I) protected with a hydrogenolysable group on the nitrogen atom may be prepared by methods analogous to those described above for formula (I).

The reaction between a compound of the formulae (III) or (IV) and a compound of the formula (V) may be performed in a suitable solvent for example an alcohol such as ethanol or propan-2-ol, at a temperature in the range for example 10°C to 110°C and most conveniently at or near the boiling-point of the reaction mixture. In the compound of the formula (IV) L may be, for example, halogen such as chloro or bromo or an arylsulphonyloxy group such as toluenesulphonyloxy or an alkanesulphonyloxy group such as methanesulphonyloxy.

The compounds of the formula (V) are prepared in any convenient manner known to those skilled in the art. For example they may be conveniently prepared by reacting compound (XIV) with a compound of the formula (XV):

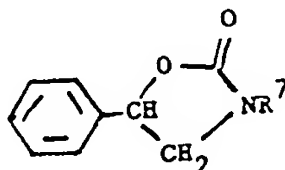


(XV)

For example this reaction may be performed using the Mitsunobu reaction with diethyl azodicarboxylate and triphenylphosphine. Desirably the amino function (and carboxy function, if present) is protected during this reaction and subsequently deprotected in conventional manner. Examples of a suitable protecting group for the amino function include the phthaloyl and t-butoxycarbonyl groups. The compounds of the formula (XV) may be prepared according to methods known in the art.

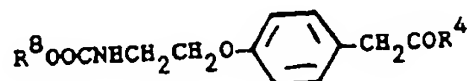
The compound of the formula (VI) may be hydrolysed to 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid or a bioprecursor thereof under conditions known in the beta adrenergic blocker art; for example via alkaline hydrolysis in a suitable solvent.

The compounds of the formula (VI) may be prepared by the reaction of a compound of the formula (XV) with a compound of the formula (XVI):



(XVI)

wherein R⁷ is a group -CH₂CH₂OH. This reaction may be performed in any conventional manner for example by a method analogous to the reaction of the compounds of the formulae (XIV) and (XV). In an alternative the compounds of the formula (VI) may be prepared by the reaction of a compound of the formula (XVI) wherein R⁷ is hydrogen with a compound of the formula (IX) as hereinbefore described. In a further alternative the compounds of the formula (VI) may be prepared by the reaction of a compound (III) with a compound of the formula (XVII):



(XVII)

wherein COR⁴ is as hereinbefore defined and R⁶O- is a leaving group, for example R⁶O- is C₁₋₄alkoxy.

The compound of the formula (XVI) wherein R⁷ is -CH₂CH₂OH may be prepared for example by reaction of a compound of the formula (III) with an N-alkoxycarbonyl derivative of a compound of the formula (XIV) wherein the hydroxy group is optionally protected for example the tetrahydropyranyl ether of t-butoxycarbonylamineethanol. The compounds of the formula (XVI) wherein R⁷ is hydrogen are obtainable in conventional manner. The compounds of the formulae (IX) and (XVII) may be obtained by alkylation of the compounds of the formula (XV) in conventional manner.

The reaction between the compounds of the formulae (VIII) and (IX) is conveniently performed under conditions analogous to the reaction between a compound (IV) and a compound of the formula (V). L' may have similar values as recited hereinabove for L.

In the compounds of the formula (VII) examples of hydrolysable groups R⁶ include C₁₋₆alkoxy and -NR¹R² groups so that -COR⁶ represents a C₁₋₆alkyl ester or an amide function. Such groups may be hydrolysed (acidic,

basic, enzymatic) to a group $-CO_2H$ under conventional conditions. Conversions wherein R^5 is an *in vivo* hydrolysable moiety also represent examples of interconversions of a bioprecursor of 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid. Suitable acid conditions are for example a strong mineral acid such as hydrochloric, sulphuric or phosphoric acid, conveniently at a temperature in the range, for example, 20° to $110^\circ C$ and in a polar solvent, such as water, a C_{1-4} alkanol (for example methanol or ethanol) or acetic acid. In such cases, the corresponding mineral acid salt of 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid may be conveniently isolated. Alternatively, base conditions may be used, for example lithium, sodium or potassium hydroxide, conveniently in a suitable solvent or diluent such as an aqueous C_{1-4} alkanol at a temperature in the range, for example, 10° to $110^\circ C$; or an alkali halide for example lithium chloride in a polar solvent such as dimethylsulphoxide. As yet further alternatives, when $-COR^5$ is *t*-butoxycarbonyl, the decomposition may be carried out, for example, by thermolysis at a temperature in the range, for example, 100 to $220^\circ C$, alone or in the presence of a suitable diluent such as diphenyl ether.

The compounds of the formula (VII) may be prepared by methods analogous to those described hereinabove for 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid or a bioprecursor thereof, with optional protection of the amino function for example with a benzyl group.

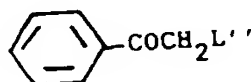
4-[2-(2-Hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid and amide bioprecursors thereof may be converted to ester precursors thereof. Suitable conditions are, for example, refluxing in the corresponding alcohol under acidic conditions, for example, with the addition of concentrated sulphuric acid as a catalyst.

The reduction of the compounds (XI), (XII) and (XIII) may be carried out by conventional chemical or catalytic methods, such as chemical reduction using sodium borohydride or by catalytic hydrogenation using catalysts such as palladium on charcoal, or platinum.

Reduction by sodium borohydride is conveniently carried out in an alcohol such as methanol and the reaction is generally carried out at from 0 - $20^\circ C$.

Catalytic reduction is conveniently carried out in a conventional hydrogenation solvent such as an alcohol, for example ethanol. The hydrogenation is generally carried out under hydrogen gas at about 1 to about 10 atmosphere pressure and at ambient or elevated temperature.

Compounds of the formula (XI) may be prepared by the reaction of a compound of the formula (V) with a compound of the formula (XVIII):



(XVIII)

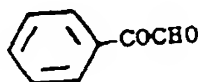
wherein L'' is a displaceable group.

The reaction between a compound of the formula (XVIII) and a compound of the formula (V) may be performed in a suitable solvent such as an alcohol or an ether, for example methanol or diethyl ether, at a temperature in the range, for example, -10 to $110^\circ C$ and most conveniently at ambient temperature. In the compounds of the formula (XVIII), L'' may be, for example, halogen such as chloro or bromo.

The resulting compounds of the formula (XI) may be converted into 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid or bioprecursors thereof *in situ*.

The compounds of the formula (XVIII) may be prepared by methods known in the art.

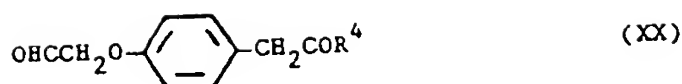
Compounds of the formula (XII) may be prepared by reacting a compound (XIX) with a compound of the formula (V):



(XIX)

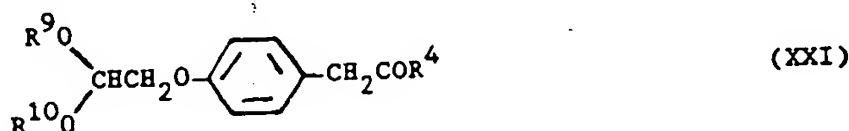
The reaction between a compound (XIX) with a compound of the formula (V) may be performed in a suitable solvent such as an alcohol, for example, ethanol at a temperature range, for example, 0 - $80^\circ C$ and most conveniently at ambient temperature. The resulting compounds of the formula (XII) may be converted into 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid or bioprecursors thereof *in situ*.

Compounds of the formula (XIII) may be prepared by reacting compounds of the formula (XX) with a compound of the formula (VIII):



wherein COR^4 is as hereinbefore defined.

The reaction between a compound of the formula (XX) and a compound (VIII) may be performed in a suitable solvent such as an alcohol, for example, ethanol, at a temperature in the range, for example, 0 - 80°C and most conveniently at ambient temperature. The resulting compounds of the formula (XIII) may be converted into 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid or bioprecursors thereof *in situ*.
Compounds of the formula (XX) may be prepared by hydrolysis of a compound of the formula (XXI):



wherein COR^4 is as hereinbefore defined and R^9 and R^{10} are independently hydrogen or C_{1-4} alkyl. Suitable conditions for hydrolysis are, for example, a strong mineral acid such as hydrochloric or sulphuric, conveniently at a temperature range, for example, 20 - 110°C, in a suitable solvent such as tetrahydrofuran, dichloromethane or diethyl ether.

Compounds of the formula (XXI) may be prepared by standard methods known in the art. For example, by reacting a compound of the formula (XXII) with a compound of the formula (XV) in the presence of a mild base:



wherein R^9 and R^{10} are as hereinbefore defined and L''' is a displaceable group.

Suitable conditions include heating in a suitable solvent such as dichloromethane, in the presence of a mild base, for example sodium carbonate. In a compound of the formula (XXII) L''' may be, for example, halogen such as bromo.

The compounds of the formulae (VI), (VII), (X), (XI), (XII) and (XIII) are novel and form another aspect of the invention.

Bioprecursor esters of the hydroxy group may be prepared in conventional manner for example by reacting the hydroxy group with an activated derivative of an acid under conditions known in the beta adrenergic blocker art.

Pharmaceutically acceptable salts may be prepared by reacting 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid or a bioprecursor thereof with the appropriate acid or base in conventional manner. Alternatively when a hydrogen halide salt is required, it may conveniently be obtained by hydrogenation of the free base together with a stoichiometric amount of the corresponding benzyl halide.

The following biological test methods, data and Examples serve to illustrate this invention.

Thermogenic effects

The thermogenic effects of compounds of the formula (I) and bioprecursors thereof may be demonstrated using one or more of the following standard tests:-

(a) Rats are cold adapted at 4°C for 5 days to increase their capacity for thermogenesis. They are then transferred to a warm environment of 25°C for 2 days. On the following day, a test compound is administered sub-cutaneously or orally. Animals are sacrificed one hour later and the interscapular, brown adipose tissue (BAT) pad is removed. BAT mitochondria are prepared by differential centrifugation and GDP binding is determined (Holloway et al., *International Journal of Obesity*, 1984, 8, 295) as a measure of thermogenic activation. Each test includes a control which is dosed with the solution/suspension vehicle only and a positive control which is dosed with isoprenaline (as its sulphate) at 1mgkg⁻¹. Test compounds are routinely dosed at 0.1, 0.3, 1.0, 3.0, and 10 mgkg⁻¹ and results expressed in terms of the effect on GDP binding

produced by the positive control. From these results, a dose (ED_{50}) necessary to produce 50% of the isoprenaline effect is calculated by curve-fitting. Compounds are considered active in this test if they cause a significant elevation in GDP binding as compared to controls.

(b) Rats are adapted to a thermoneutral environment (29°C) for 2 weeks in order to decrease their capacity for BAT mediated non-shivering thermogenesis. During the final 5 days the animals are trained to use an apparatus for measuring heart rate non-invasively via foot-pad electrodes connected to an ECG integrator giving a continuous read-out of heart rate. A test compound is administered sub-cutaneously or orally at the ED_{50} determined in test (a), and heart rate is determined 15-30 minutes after dosing. The procedure is then repeated in subsequent tests using increasing multiples of the ED_{50} determined in test (a) until the heart rate (HR) reaches or exceeds 500 beats per minute, or until the dose reaches 100 times the ED_{50} determined in test (a). The dose necessary to produce a heart rate of 500 beats per minute (D_{500} dose) is estimated.

The ratio of D_{500} to ED_{50} in test (a) can be defined as the selectivity index (SI) and provides a measure of the selectivity of the compound for BAT as opposed to the cardiovascular system. Compounds are considered to have significant selectivity which have an SI of >1 . Non-selective compounds have an SI of <1 (for example isoprenaline = 0.06).

(c) Rats are kept at 23°C for at least two days, then fasted overnight. On the following day, the basal metabolic rate of the animals is determined using a close-circuit oxygen consumption apparatus of the type described by Arundel et al., 1984, *J. Appl. Physiol. Respirat. Environ. Exercise Physiol.*, 1984, **57** (5) 1591-1593. The rats are then dosed (orally) with test compound at about 1 mg kg^{-1} as a solution or suspension in 0.025% w/v Polysorbate 80 (0.5ml/100g). Metabolic rate is then determined for at least one hour after dosing. Compounds are considered active in this test if they cause a significant increase in metabolic rate as compared to control animals (Student's t test: $p < 0.05$) dosed only the solution or suspension vehicle. In the above tests, the compounds of the formula (I) in general produce effects of the following order without

producing overt toxicity:-

test (a): sub-cutaneous or oral ED_{50} for GDP binding in BAT mitochondria of $0.01-10 \text{ mg kg}^{-1}$;

test (b): show an SI of >50 ; and

test (c): show $2-9 \text{ ml O}_2 \text{ min}^{-1} (\text{Kg}^{0.75})^{-1}$ at $1 \text{ mg kg}^{-1} \text{ p.o.}$

By way of illustration, the compound described in the accompanying Example 1, produces the following effects in the above tests:-

(a) oral ED_{50} 0.55 mg kg^{-1} ;

(b) SI >50 (oral);

(c) $6.53 \text{ ml O}_2 \text{ min}^{-1} (\text{Kg}^{0.75})^{-1}$ at $1 \text{ mg kg}^{-1} \text{ p.o.}$

Oral glucose tolerance test

Male rats (125-150g) were fasted for 24 hours. After fasting, a group of six rats was anaesthetised and a cardiac blood sample taken. Other groups of rats were then dosed with the compound of Example 1 (5.0 mg/Kg p.o.) dissolved in an aqueous solution of 0.025% polysorbate. Control rats were dosed with polysorbate solution alone. The volume of solution dosed was 0.5 ml/100g body weight. 60 minutes subsequent to dosing six control and six treated rats were anaesthetised and cardiac samples taken. The remaining rats were given an oral glucose load (1 g/Kg) dosed as a 20% solution of D-glucose (0.5 ml/100g). Groups of six rats for each control and treatment were then anaesthetised and bled at 20, 60 and 120 minutes after the glucose load. Plasma glucose and insulin were determined using standard methods.

ResultsPlasma glucose (mM)

5	Time relative to oral glucose load (mins)	Plasma glucose (mM)	
		Control	Example 1 5mg/Kg p.o.
	-30	6.35±0.26	
10	0	6.13±0.21	3.52±0.07 (p<0.001)
	20	9.05±0.50	5.72±0.24 (p<0.001)
15	60	6.37±0.39	5.32±0.24 (p<0.05)
20	120	6.5 ±0.23	5.43±0.31 (p<0.05)

25 The results are mean ± S.E.M. of observations in six rats in each group. Student's t test was used to test the significance of the difference between control and treated groups. The compound of Example 1 possesses marked antihyperglycaemic activity.

Effects on blood glucose levels in insulin resistant db/db mice

30 C57BL/KsJ (db/db) mice were divided into two groups and allowed free access to control diet or diet containing the compound of Example 1 at a concentration of 50mg/kg diet. A group of control (+/+) mice was also included in the experiment. After 16 days treatment, blood samples were taken from the mice for determination of blood glucose levels.

Results

	<u>Group</u>	<u>Blood glucose (mM)</u>
40	Control (+/+)	4.94±0.1
	Untreated (db/db)	14.53±0.66 (p<0.001)
45	Compound of Example 1 (db/db)	5.3±0.46

50 Results are mean ± S.E.M. of observations in groups of 15 mice. Student's t test was used to test the significance of the difference between control (+/+) and treated (db/db) groups. The compound of Example 1 normalises blood glucose levels in this animal model of insulin resistance.

Rat adipocyte lipolysis test

55 Epididymal adipose tissue was excised from male rats and adipocytes prepared by digestion with collagenase. Cells were isolated by flotation and washed four times with Krebs Ringer Bicarbonate buffer (KRB), finally washing in KRB containing 2% bovine serum albumin (KRB/BSA). Aliquots of the cell suspension were incu-

bated in the presence of a range of concentrations of the test compound in a total volume of 1ml KRB/ 2% BSA containing 0.1 mg/ml ascorbate in an atmosphere of 95%O₂,5%CO₂. Incubations were also carried out in the presence of a concentration of isoprenaline (3×10^{-6} M) known to have a maximal effect on lipolysis. Control incubations were carried out in KRB/ 2% BSA containing ascorbate. The incubations were terminated after 90 minutes by placing the tubes on ice, and aliquots of intranant removed for assay of free fatty acids which were measured using a WAKO NEFA-C assay kit (Alpha Laboratories). Lipolytic activity of the compounds was assessed by determining the increase in free fatty acid concentrations caused by the compounds compared to controls. The maximal effects (efficacy) of the compounds were determined and expressed as percentage of the maximal effect of isoprenaline.

<u>Test compound</u>	<u>Efficacy</u>
Compound of Example 1	100X
4-[2-(2-Hydroxy-3-phenoxypropylamino)-ethoxy]phenoxyacetic acid (free carboxylic acid from USP4772631)	26X

Efficacy is the maximal effect of the test compound on lipolysis expressed as a percentage of the maximal effect of isoprenaline.

Comparative test on GDP potency

In another comparative test the potency of the compound of Example 1 in test a) above was compared with a reference compound

<u>Compound</u>	<u>ED₅₀ (oral)</u> <u>mgkg⁻¹</u>
Example 1	0.55
4-[2-(2-Hydroxy-2-phenylethyl-amino)ethoxy]phenyloxyacetic acid (within the scope of EP-A 23385)	>3.00

The invention will now be illustrated by the following Examples in which, unless otherwise stated:
 a) chromatography was performed on Kieselgel (Art 9385; 230-400 Mesh) obtainable from E. Merck, Darmstadt, Federal Republic of Germany.
 b) evaporations were carried out under reduced pressure using a rotary evaporator.
 c) melting-points are uncorrected.

Example 1

(R)-4-[2-(2-Hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid

(R)-4-[2-(2-Hydroxy-2-phenylethylamino)ethoxy]phenylacetamide hydrochloride (3.5g) was heated on the steam bath for two hours in 2N HCl (100ml). The reaction mixture was filtered, cooled and the solid collected by filtration. The solid was crystallised from water to give (R)-4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid as the hydrochloride (2.5g), mp 207-209°C; microanalysis: found C, 61.5, H, 6.5; N, 3.8; Cl, 10.1%; required for C₁₈H₂₂ClNO₄: C, 61.5; H, 6.3; N, 4.0; Cl, 10.1%; $[\alpha]_D^{25} = -27.3^\circ$ (c = 0.99 in methanol).

The product hydrochloride described above (1g) was dissolved in distilled water (50ml) at room temperature and then the pH was carefully adjusted to pH 6.7 by the addition of 2N NaOH. The solid which separated was (R)-4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid (0.8g), m.p. 209-211°C; microanalysis: found, C, 68.4; H, 6.8; N, 4.5%; required for $C_{18}H_{21}NO_4$: C, 68.6; H, 6.7; N, 4.5% $[\alpha]^{25}_D = -30.1^\circ$ (c, 1.0 in acetic acid).

In an alternative, the product may be obtained by acid hydrolysis, in similar manner to that above, of (R)-4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetamide with recrystallisation from water.

Example 2

(R)-4-[2-(2-Hydroxy-2-phenylethylamino)ethoxy]phenylacetamide

(R)-4-[2-(N-Benzyl-N-(2-hydroxy-2-phenylethyl)amino)ethoxy]phenylacetamide (12.9g) was dissolved in ethanol (150ml) and glacial acetic acid (50ml). The solution obtained was hydrogenated in the presence of 10% w/w palladium on carbon (1.0g) at about 20 bar and 60° for 24 hours. The mixture was cooled, filtered and the filtrate was evaporated under reduced pressure. 1.2g of the residual oil (9.8g) thus obtained was dissolved in ethyl acetate and treated with a solution of ether saturated with hydrogen chloride. The precipitated solid was crystallised from methanol to give (R)-4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetamide hydrochloride (0.8g), mp 255-257°C; microanalysis: found C, 61.3; E, 6.3; N, 8.0; Cl, 10.2% required for $C_{18}E_{22}ClN_2O_3$: C, 61.6; H 6.6; N, 8.0; Cl, 10.1%; $[\alpha]^{25}_D = -19.5^\circ$ (c = 1.0 in DMSO). This reaction may also be performed in aqueous isopropanol containing glacial acetic acid (1 equivalent) at ambient temperature and pressure.

The starting material was prepared as follows:

A mixture of 4-[2-(benzylamino)ethoxy]phenylacetamide (OLS 2135678) (14.0g), (R)-styrene oxide (5.92g) and propan-2-ol (200ml) was heated under reflux for 72 hours. The mixture was cooled and the solvent evaporated under reduced pressure. The residue was purified by dry, flash column chromatography. Elution with 10% methanol in dichloromethane gave (R)-4-[2-(N-benzyl-N-(2-hydroxy-2-phenylethyl)amino)ethoxy]phenylacetamide as an oil (12.9g). This reaction may also be performed in t-amyl alcohol under reflux.

Example 3

(R)-Methyl 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetate

(R)-4-[2-(2-Hydroxy-2-phenylethylamino)ethoxy]phenylacetamide hydrochloride (0.45g) was heated under reflux in methanol (20ml) containing concentrated sulphuric acid (0.5ml) for 18 hours. The mixture was cooled and the solvent evaporated under reduced pressure. The residue was dissolved in dichloromethane (30ml) and washed successively with water (20ml), 5% $NaHCO_3$ solution (50ml) and water (20ml), dried over $MgSO_4$ and then the solvent was removed under reduced pressure. The residue was dissolved in methyl acetate (20ml) and treated with a solution of ether saturated with hydrogen chloride. The precipitated solid was crystallised from a mixture of methanol and methyl acetate to give (R)-methyl 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetate hydrochloride (0.25g), m.p. 181-183°C; microanalysis: found, C, 62.6; H, 6.6; N, 3.8; Cl, 9.9%; required for $C_{19}H_{24}ClNO_4$: C, 62.4; H, 6.6; N, 3.8; Cl, 9.7%; $[\alpha]^{25}_D = -25.3^\circ$ (c = 0.99 in methanol).

Example 4

4-[2-(2-Hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid

4-[2-(2-Hydroxy-2-phenylethylamino)ethoxy]phenylacetamide hydrochloride (2.8g) was heated on the steam-bath for 4 hours in 4N HCl (60ml). The reaction mixture was filtered, cooled and the solid collected by filtration was 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid as the hydrochloride (1.4g), m.p. 183-184°C (softens at about 178°C); microanalysis: found C, 61.4; H, 6.3; H, 4.1; Cl, 10.3%; required for $C_{18}H_{22}ClNO_4$: C, 61.5; H, 6.3; N, 4.0; Cl 10.1%.

Example 5

4-[2-(2-Hydroxy-2-phenylethylamino)ethoxy]phenylacetamide

A preformed solution of 4-[2-(N-benzyl-N-(2-hydroxy-2-phenylethyl)amino)ethoxy]phenylacetamide in

propan-2-ol and glacial acetic acid (see below) was hydrogenated in the presence of 10% w/w palladium on carbon (1.0g) at about 20 bar and 60°C for 12 hours. The mixture was cooled, filtered and the filtrate was evaporated under reduced pressure. The residual oil thus obtained was dissolved in ethyl acetate and treated with a solution of ether saturated with hydrogen chloride. The precipitated solid was crystallised from methanol to give 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetamide hydrochloride (6.8g), m.p. 250-251°C (softens at about 248°C); microanalysis: found C, 61.2; H, 6.5; N, 8.3; Cl, 10.3%; required for $C_{18}H_{23}ClN_2O_3$: C, 61.6; H, 6.6; N, 8.0; Cl, 10.1%.

The starting material was prepared as follows:

A mixture of 4-(2-N-benzylaminoethoxy)phenylacetamide (CLS 2135678) (5.68g), styrene oxide (2.4g) and propan-2-ol (100ml) was heated under reflux for 72 hours. The thus formed 4-[2-(N-benzyl-N-(2-hydroxy-2-phenylethyl)amino)ethoxy]phenylacetamide was cooled and diluted with propan-2-ol (30ml) and glacial acetic acid (20ml).

An alternative method for preparing the title compound is:

2-Hydroxy-2-phenylethylamine (1.91g), 4-(2-bromoethoxy)phenylacetamide (3.59g) and triethylamine (1.41g) in ethanol (450ml) were heated under reflux for 24 hours and then the solution was cooled and filtered to remove a little insoluble material (0.2g). The solvent was removed from the filtrate under reduced pressure and the residual solid was triturated with a little water, isolated by filtration and dried. The solid (3.1g) was dissolved in methanol (100ml) and treated with a solution of ether saturated with hydrogen chloride. The precipitated solid was crystallised from methanol to give 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetamide hydrochloride m.p. and mixed m.p. 250-251°C.

A further alternative method for preparing the title compound is:

Phenacyl bromide (0.49g), 4-(2-aminoethoxy)phenylacetamide (0.49g), potassium carbonate (0.35g) and methanol (20ml) were heated under reflux for 2 hours, cooled to ambient temperature and stirred whilst sodium borohydride (1.0g) was added in small portions during 1 hour. Stirring was continued for 18 hours and then the solvent was evaporated under reduced pressure. The residue was partitioned between dichloromethane (20ml) and water (10ml). The aqueous layer was separated and extracted with dichloromethane (20ml). The combined dichloromethane extracts were washed with water (20ml), dried over $MgSO_4$ and evaporated. The residual gum was dissolved in ethyl acetate and treated with a solution of ether saturated with hydrogen chloride. The precipitated solid was crystallised from a mixture of methanol and ethyl acetate to give 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetamide hydrochloride m.p. and mixed m.p. 248-250°C.

A yet further alternative method for preparing the title compound is:

Phenylglyoxal hydrate (0.57g) and 4-(2-aminoethoxy)phenylacetamide (0.49g) in methanol (15ml) were heated on the steam bath to obtain a clear solution. This was then cooled in an ice-bath and sodium borohydride (1g) was added in small portions during 1 hour with stirring. After about 100mg of sodium borohydride had been added a white solid began to separate and this was redissolved by the addition of further methanol (35ml). The mixture was stirred at ambient temperature for 18 hours and then the solvent was evaporated under reduced pressure. The residual solid was treated with dichloromethane (20ml) and water (20ml) and that solid which did not go into solution was isolated by filtration. This solid was dissolved in methanol (20ml) and treated with a solution of ether saturated with hydrogen chloride. The bulk of the solvent was evaporated and ethyl acetate (20ml) was added to precipitate the title compound as hydrochloride m.p. and mixed m.p. 250-251°C.

Example 6

Methyl 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetate

4-[2-(2-Hydroxy-2-phenylethylamino)ethoxy]phenylacetamide hydrochloride (2.5g) was heated under reflux in methanol (50ml) containing concentrated sulphuric acid (1.5ml) for 24 hours. The mixture was cooled and the solvent evaporated under reduced pressure. The residue was partitioned between dichloromethane (150ml) and 5% $NaHCO_3$ solution (150ml). The organic layer was separated and washed successively with 5% $NaHCO_3$ solution (20ml) and water (20ml), dried over $MgSO_4$ and then the solvent was removed under reduced pressure. The residue was dissolved in methyl acetate (40ml) and treated with a solution of ether saturated with hydrogen chloride. The precipitated solid was crystallised from a mixture of methanol and methyl acetate to give methyl 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetate hydrochloride (1.8g), m.p. 169-171°C; microanalysis: found C, 62.5; H, 6.6; N, 3.8; Cl, 9.7%; required for $C_{19}H_{24}ClNO_4$: C, 62.4; H, 6.6; N, 3.8; Cl, 9.7%.

Example 7

(R)-4-[2-(2-Acetoxy-2-phenylethylamino)ethoxy]phenylacetic acid

A solution of N-t-butoxycarbonyl-(R)-4-[2-(2-acetoxy-2-phenylethylamino)ethoxy]phenylacetic acid (500mg) in a mixture of dichloromethane (5ml) and trifluoroacetic acid (5ml) was allowed to stand for 90 minutes at 20°C. The solvent was removed under reduced pressure and the residue was dissolved in ethanol (5ml). The solution was cooled to -20°C and ethereal hydrogen chloride was added to yield white crystals of the title compound as the hydrochloride (300mg); m.p. 158-160°C; $[\alpha]^{25}_D = -35.4^\circ$ (c = 1.0 in methanol); microanalysis: found C, 60.2; H, 6.5; N, 3.4; H₂O, 0.9%; required for C₂₀H₂₄ClNO₅ 0.25 H₂O: C, 60.3; H, 6.2; N, 3.5; H₂O 1.1%.

The starting material was prepared as follows:

a) Di-t-butyl dicarbonate (1.25g) in t-butanol (15ml) was added to a stirred solution of (R)-4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid hydrochloride (2.0g) in 1N aqueous sodium hydroxide (30ml). The reaction mixture was stirred for 90 minutes at 20°C. The solvent was removed under reduced pressure. Water (20ml) was added to the residue and the solution was acidified with 2N aqueous citric acid. The product was extracted into 5% methanol in dichloromethane (5 x 20ml). The extracts were dried and the solvent removed under reduced pressure to yield N-t-butoxycarbonyl-(R)-4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid as a glass (1.3g); $[\alpha]^{25}_D = +6.2^\circ$ (c = 1.0 in methanol).

b) A solution of the product from a) above in pyridine (2.5ml) and acetic anhydride (2.5ml) was allowed to stand for 16 hours at 20°C. The solvent mixture was removed under reduced pressure. The residue was dissolved in dichloromethane (20ml). The solution was washed with water (3 x 10ml), dried, and the solvent removed under reduced pressure to give a viscous oil (1.3g). A solution of the oil (1.3g) in a mixture of dioxan (10ml) and water (6ml) was stirred under reflux for 2 hours. The solvent was removed under reduced pressure and the residue was subjected to chromatography using 10% methanol in dichloromethane as eluant. The appropriate fractions were combined to yield N-t-butoxycarbonyl-(R)-4-[2-(2-acetoxy-2-phenylethylamino)ethoxy]phenylacetic acid as a viscous oil (500mg); $[\alpha]^{25}_D = -16.8^\circ$ (c = 1.0 in dichloromethane).

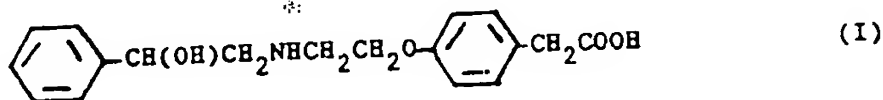
Example 8

As stated previously, suitable pharmaceutical compositions of compounds of formula (I) defined hereinbefore may be obtained by standard formulation techniques.

A typical tablet formulation suitable for oral administration to warm-blooded animals comprises as active ingredient a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore (for example as described in one of the preceding Examples), and may be produced by aqueous granulation or direct compression together with milled lactose containing a standard disintegrant and/or lubricant. When tablets containing small amounts of active ingredient (for example 0.5-10 mg) are required, the direct compression method may be used wherein the active ingredient is mixed with lactose in the ratio of 1:10 parts by weight and/or microcrystalline cellulose containing 0.5% by weight of a lubricant (such as magnesium stearate) and 5% by weight of a disintegrant (such as cross-linked sodium carboxymethyl cellulose or sodium starch glycolate). An example of a tablet prepared by aqueous granulation is that containing active ingredient (50-100mg), lactose (230mg), maize starch (80mg), gelatine (2.2mg), magnesium stearate (4mg) and croscarmellose sodium (7mg).

Claims

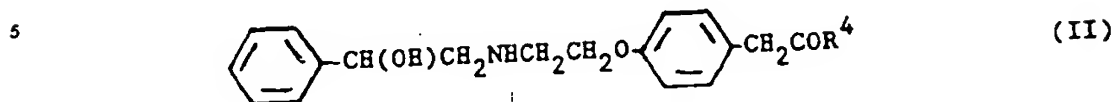
1. A compound of the formula (I):



or a bioprecursor or a pharmaceutically acceptable salt thereof.

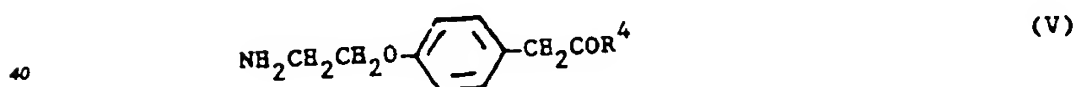
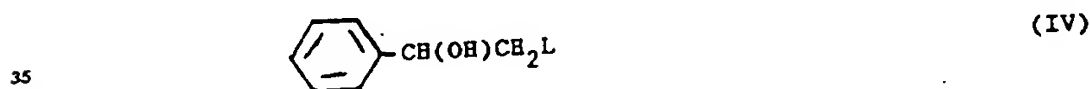
2. A compound according to claim 1 when in the form of a carboxylic acid or pharmaceutically acceptable salt thereof.

3. A compound according to claim 2 in the form of a salt formed with hydrochloric acid.
 4. A compound according to claim 1 of the formula (II):

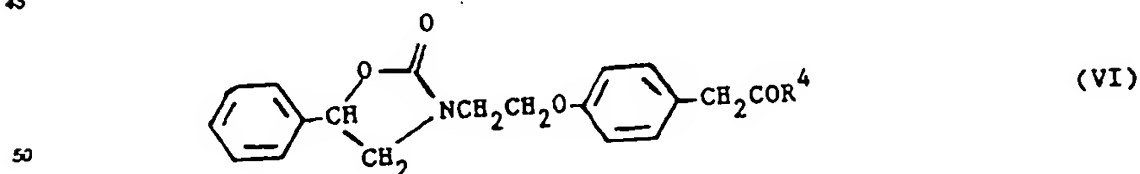


10 wherein R^4 is C_{1-6} alkoxy, or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 4 wherein R^4 is methoxy.
 6. A compound according to claim 1 which is:
 15 (R)-4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid;
 (R)-4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetamide;
 (R)-methyl 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetate;
 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid;
 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetamide; or
 20 methyl 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetate;
 or a pharmaceutically acceptable salt thereof.
 7. A pharmaceutical composition which comprises a compound according to claim 1 or a bioprecursor or
 pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.
 25 8. A process for preparing a compound according to claim 1 which process comprises:
 a) reacting a compound (III) or (IV) with a compound of the formula (V):



45 wherein $-\text{COR}^4$ is carboxy or its bioprecursor and L is a displaceable group; or
 b) hydrolysis of a compound of the formula (VI):

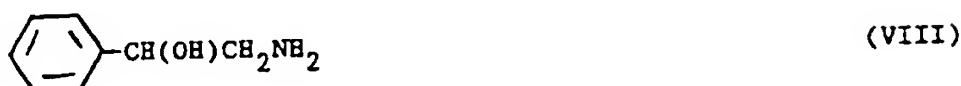


55 wherein COR^4 is as hereinbefore defined; or
 c) for 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid hydrolysing a compound of the for-
 mula (VII):



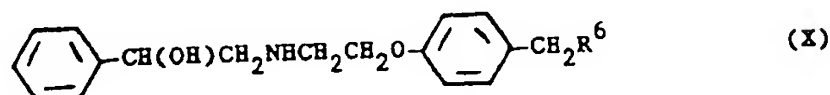
wherein R^5 is a hydrolysable group;

d) reacting a compound of the formula (VIII) with a compound of the formula (IX):



wherein $-\text{COR}^4$ is as hereinbefore defined and L' is a displaceable group;

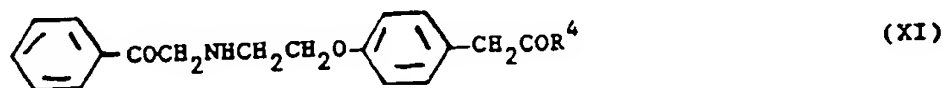
e) deprotecting a compound of the formula (X):



wherein R^6 is a protected derivative of a group $-\text{COR}^4$;

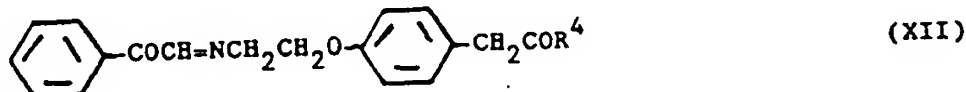
f) converting 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid into a bioprecursor, or vice versa, or converting a bioprecursor of 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid into another bioprecursor of 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid;

g) reducing a compound of the formula (XI):



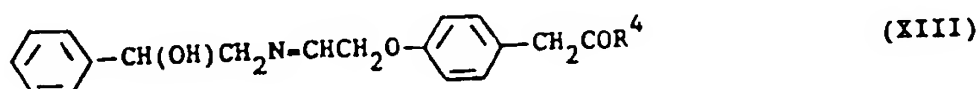
wherein $-\text{COR}^4$ is as hereinbefore defined;

h) reducing a compound of the formula (XII):



wherein $-\text{COR}^4$ is as hereinbefore defined;

i) reducing a compound of the formula (XIII):



wherein COR^4 is as hereinbefore defined;

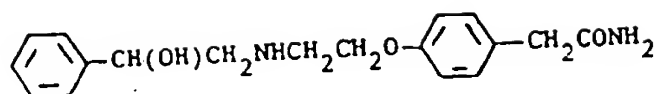
and wherein any functional group is optionally protected and thereafter if necessary;

(i) removing any protecting groups;

(ii) forming a pharmaceutically acceptable salt.

9. A compound of the formula (VI), (X), (XI), (XII) or (XIII) as defined in claim 8.

10. A compound of the formula:



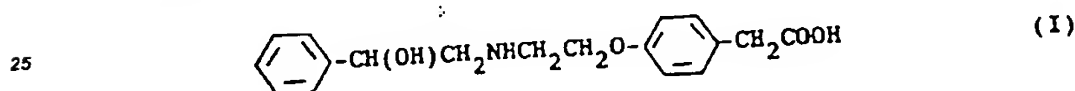
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11. The use of a compound according to claim 1 or a bioprecursor or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating disease conditions mediated through β_3 -adrenoceptors.
12. The use of a compound according to claim 1 or a bioprecursor or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for stimulating thermogenesis and/or improving glucose tolerance.
13. The use of a compound according to claim 1 or a bioprecursor or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating obesity, mature onset diabetes, NIDDM, hypertension and/or hyperlipidaemia.
14. The use of a compound according to claim 1 or a bioprecursor or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating hypertriglyceridaemia, hypercholesterolaemia, atherosclerotic disease and conditions of low HDL levels.

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20 Claims for the following Contracting States : GR, ES

1. A process for preparing a compound of the formula (I):



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or a bioprecursor or a pharmaceutically acceptable salt thereof, which process comprises:
a) reacting a compound (III) or (IV) with a compound of the formula (V):

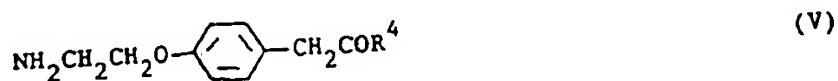
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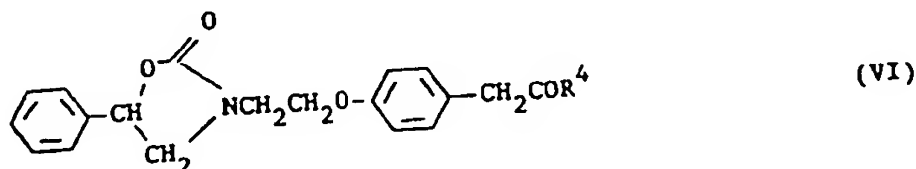
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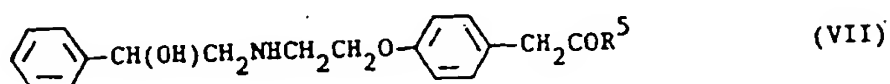
wherein $-\text{COR}^4$ is carboxy or its bioprecursor and L is a displaceable group; or
b) hydrolysis of a compound of the formula (VI):

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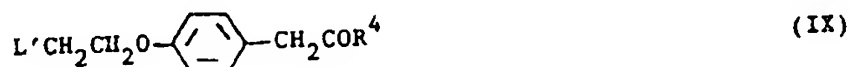
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wherein COR^4 is as hereinbefore defined; or
c) for 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid hydrolysing a compound of the formula (VII):

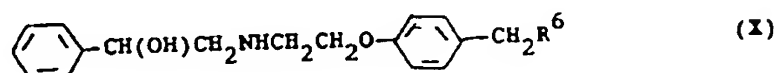


wherein R^5 is a hydrolysable group;

d) reacting a compound of the formula (VIII) with a compound of the formula (IX):

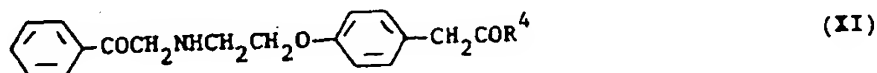


wherein $-\text{COR}^4$ is as hereinbefore defined and L' is a displaceable group;
e) deprotecting a compound of the formula (X):



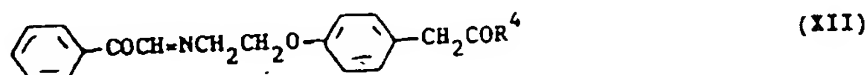
wherein R^6 is a protected derivative of a group $-\text{COR}^4$;

f) converting 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid into a bioprecursor, or vice versa, or converting a bioprecursor of 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid into another bioprecursor of 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid;
g) reducing a compound of the formula (XI):



wherein $-\text{COR}^4$ is as hereinbefore defined;

h) reducing a compound of the formula (XII):



wherein $-\text{COR}^4$ is as hereinbefore defined;

i) reducing a compound of the formula (XIII):



wherein COR^4 is as hereinbefore defined;

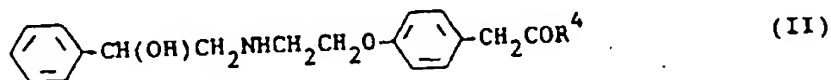
and wherein any functional group is optionally protected and thereafter if necessary;

(i) removing any protecting groups;

(ii) forming a pharmaceutically acceptable salt.

2. A process according to claim 1 for preparing a compound in the form of a carboxylic acid or pharmaceutically acceptable salt thereof.
3. A process according to claim 2 for preparing a compound in the form of a salt formed with hydrochloric acid.

4. A process according to claim 1 for preparing a compound of the formula (II):



wherein R^4 is C_{1-6} alkoxy, or a pharmaceutically acceptable salt thereof.

5. A process according to claim 4 for preparing a compound wherein R^4 is methoxy.

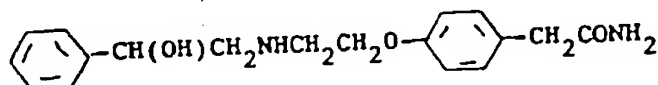
6. A process compound according to claim 1 for preparing a compound which is:

(R)-4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid;
 (R)-4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetamide;
 (R)-methyl 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetate;
 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetic acid;
 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetamide; or
 methyl 4-[2-(2-hydroxy-2-phenylethylamino)ethoxy]phenylacetate;
 or a pharmaceutically acceptable salt thereof.

7. A process for preparing a pharmaceutical composition which comprises bringing into association a compound of the formula (I) as defined in claim 1 or a bioprecursor or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

8. A compound of the formula (VI), (X), (XI), (XII) or (XIII) as defined in claim 1.

9. A compound of the formula:



10. The use of a compound of the formula (I) as defined in claim 1 or a bioprecursor or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating disease conditions mediated through β_3 -adrenoceptors.

11. The use of a compound of the formula (I) as defined in claim 1 or a bioprecursor or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for stimulating thermogenesis and/or improving glucose tolerance.

12. The use of a compound of the formula (I) as defined in claim 1 or a bioprecursor or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating obesity, mature onset diabetes, NIDDM, hypertension and/or hyperlipidaemia.

13. The use of a compound of the formula (I) as defined in claim 1 or a bioprecursor or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating hypertriglyceridaemia, hypercholesterolaemia, atherosclerotic disease and conditions of low HDL levels.